

N of 1 trials

Managing patients with chronic fatigue syndrome: two case reports

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SUMMARY

Chronic fatigue syndrome is a heterogeneous condition with no proven effective treatment. I present two case reports in which N of 1 trials helped me make management decisions. High-dose vitamin B₁₂ injections were ineffective in one case; nimodipine was very effective in the other case.

RÉSUMÉ

Le syndrome de fatigue chronique est une affection hétérogène contre laquelle aucun traitement n'est efficace. Je vous présente deux études de cas où des essais N de 1 m'ont facilité la prise de décisions thérapeutiques. Des injections de fortes doses de vitamine B₁₂ furent inefficaces dans l'un des cas. Par contre, la nimodipine fut très efficace dans l'autre cas.

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FAMILY DOCTORS FIND IT VERY frustrating to treat patients with chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME). The first problem is diagnosis. The Centers for Disease Control (CDC) has specific criteria for these diseases (*Table 1*),¹ but no biochemical measurements are useful. In general practice, the prevalence of CFS is 27%, unexplained chronic fatigue 8.5%, and symptoms meeting CDC criteria for CFS 0.3%.² Patients with CFS meeting CDC criteria and patients with unexplained chronic fatigue appear to be a heterogeneous group with many overlapping physical and psychiatric symptoms.

The second problem is treatment. No good, double-blind, placebo-controlled trials have shown any treatment to be effective. The US public health service pamphlet for physicians, entitled *Chronic Fatigue Syndrome*, says, "In the absence of any proven treatments, empiric therapies should be tried. At the same time, patients

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need to be kept from using untested remedies which may hurt them."³ This puts physicians in a very difficult position.

The third problem is the attitudes of both patients and physicians. Patients turn to support groups and are given literature that encourages self-diagnosis and advises how to approach a physician who "doesn't believe in ME." Physicians think that patients who self-diagnose ME or CFS are likely to be difficult, noncompliant, and time-consuming.⁴

I report on two patients I treated by using N of 1 trials to help with management decisions.

Case 1

A 45-year-old woman worked as an administrator in a government office. In July 1991, she developed a severe sore throat with lymphadenopathy. I diagnosed mononucleosis on the basis of a positive spot test for infectious mononucleosis and clinical findings. She could not work for 4 months and then worked part time during 1992. Her symptoms included fatigue, post-exercise malaise, cognitive impairment, and insomnia. She was investigated thoroughly by two

infectious disease specialists and a CFS clinic. She was not clinically depressed. She joined an ME support group and, in July of 1992, asked me to start injecting her with 3000 µg of vitamin B₁₂ twice weekly.

A double-blind, placebo crossover trial, using 200 µg daily in 14 patients, had shown no effect,⁵ but no reported trials had used the dose my patient requested. I reluctantly agreed to give her the injections. She said she improved and insisted on continuing. I felt like a quack but, as I had nothing better to offer her, I continued. After 1 year I remained sceptical and uncomfortable about the injections and asked her to participate in an N of 1 trial.

A pharmacist provided the filled opaque syringes for each appointment so that neither my patient nor I were aware of whether vitamin B₁₂ or saline was being injected. My patient and I drew up scales for the symptoms she felt were most disabling and most helped by the injections. We used part of the Mini-Mental State Examination⁶ to assess cognitive impairment and self-reporting on scales of 1 to 10 for energy, sleep, and "mental fog." We used four periods of 1½ weeks each (three injections), crossing over between placebo and drug. This timing was chosen on the basis of the patient's perception of her reaction to the injections. Results (*Table 2*) showed that the injections had no effect. The patient accepted these results and stopped the injections. She recovered from her CFS symptoms about 6 months later and currently has a full, active life.

Case 2

A 25-year-old woman was doing graduate work at the university and working part time when she became ill in the fall of 1993. She complained of severe fatigue: a 15-minute walk caused her to be in bed the next day. She had difficulty reading or concentrating, insomnia, generalized aching, and nausea. She had frequent flares of viral symptoms, including lymphadenopathy. She was not clinically depressed. She was fully investigated by an infectious disease specialist and diagnosed with ME.

Table 1. Definition of chronic fatigue syndrome

According to the Centers for Disease Control,¹ a case of chronic fatigue syndrome must fulfil the two major criteria and six or more of the 11 symptom criteria and two or more of the three physical criteria, or eight or more of the 11 symptom criteria. To fulfil the criteria, symptoms must have begun at or after the onset of increased fatigability and must have persisted or recurred for at least 6 months (individual symptoms might not occur simultaneously). Physical criteria must be documented by a physician on at least two occasions at least 1 month apart.

MAJOR CRITERIA

1. New onset of persistent or relapsing, debilitating fatigue or easy fatigability in a person with no previous history of similar symptoms, that does not resolve with bed rest, and that is severe enough to reduce or impair average daily activity below 50% of the patient's premorbid activity level for at least 6 months
2. Other clinical conditions that could produce similar symptoms must be excluded by thorough evaluation, based on history, physical examination, and appropriate laboratory findings.

MINOR CRITERIA

Symptom criteria

1. Mild fever with an oral temperature between 37.5°C and 38.6°C, if measured by the patient, or chills
2. Sore throat
3. Painful lymph nodes in the anterior or posterior cervical or axillary distribution
4. Unexplained generalized muscle weakness
5. Muscle discomfort or myalgia
6. Prolonged (24 hours or longer), generalized fatigue after levels of exercise easily tolerated in the patient's premorbid state
7. Generalized headaches of a type, severity, or pattern different from headaches experienced in the premorbid state
8. Migratory arthralgia without joint swelling or redness
9. Neuropsychologic complaints: one or more of photophobia, transient visual scotomata, forgetfulness, excessive irritability, confusion, difficulty thinking, inability to concentrate, depression
10. Sleep disturbance (hypersomnia or insomnia)
11. Describing the main symptom complex as initially developing over a few hours to a few days (not a true symptom, but may be considered equivalent to the above symptoms in meeting the requirements of the case definition)

Physical criteria

1. Low-grade fever with oral temperature between 37.6°C and 38.6°C or rectal temperature between 37.8°C and 38.8°C
2. Nonexudative pharyngitis
3. Palpable or tender anterior or posterior cervical or axillary lymph nodes

In spring 1995, she gave me the list of drugs she wanted to try (*Table 3*). I decided the least obnoxious one was nimodipine. I was unfamiliar with this drug but discovered it was a calcium channel blocker approved for use in patients with subarachnoid hemorrhage. It was also found effective for senile dementia.⁷ I agreed to try it if she would agree to an N of 1 study. A pharmacist prepared "bubble packs" of nimodipine (30 mg) and placebos in six blocks of 3 days each so that neither the patient nor I were aware of which she was taking.

The patient kept a diary of her main symptoms using a 0 to 10 scale to rate them. Results (*Table 4*) were striking, showing marked improvements in fatigue, cognitive ability, and myalgia. She continues to take nimodipine. She appears to be fully recovered, is back to work, and is active in her leisure time.

Discussion

These two N of 1 trials did not prove that vitamin B₁₂ injections are ineffective and nimodipine is effective for treating CFS. The trials

Table 2. Mean symptom scores at end of each crossover period in case 1

SYMPTOMS*	VITAMIN B ₁₂	PLACEBO
Serial 7s	4.5	4.5
Energy	3.25	4.0
Mental "fog"	8.25	7.5
Sleep	3.25	3.25

*Serial 7s on Mini-Mental State Examination, out of 5. Energy, mental fog, and sleep on a scale of 1 to 10 where 1 is "bad" and 10 is "good."

Table 4. Mean symptom scores at end of each crossover period in case 2

SYMPTOMS*	NIMODIPINE	PLACEBO
Sleep	3.0	7.0
Muscle pain	2.0	7.67
Mental "fog"	1.0	7.0
Fatigue	1.3	7.67

*On a 0 to 10 scale, for sleep, 0 was solid restful sleep and 10 was very disrupted, often wakeful; for muscle pain, 0 was no pain and 10 was "I could just cry"; for mental fog, 0 was very clear-headed and 10 was low concentration and high confusion; and for fatigue, 0 was a lot of energy and 10 was lying down all day.

Table 3. Medication list provided by patient in case 2

Naphazoline HCL 0.1% gtt 1 OU qid
Nitroglycerin 0.04 mg subling qid
Nimodipine 30 mg qid
Gabapentin 100-300 mg tid
Oxytocin 5-10 U IM OD or BID
Pyridostigmine 30-60 mg po qid
Hydralazine 10-25 mg po tid
Baclofen 10 mg tid
Mexilitine 150 mg po tid
Tacrine 10 mg qid
Risperidone 0.25-0.5 mg bid
Pindolol 5 mg bid
Sumatriptan 3-6 mg bid
Ranitidine 150 mg bid
Doxepin HCL elixir 2-20 mg hs
Sertraline 25-50 mg od
Bupropion 100 mg tid
Venlafaxine 37.5-75 mg bid
Glycine powder 0.4 gm/kg/day in juice
Felbamate 400 mg tid

helped me and my patients make the appropriate management decisions in their cases. It made me feel better (less like a quack) to use a scientific method to choose therapy.

N of 1 trials might be useful for managing other medical conditions. They have been used successfully to determine which patients with osteoarthritis benefit from the more expensive nonsteroidal anti-inflammatory drugs and which need only acetaminophen.⁸

Chronic fatigue syndrome is a costly condition, in terms of both patients' suffering and insurance claims for loss of work. It makes sense that we try, in a scientific manner, some of the unproven empiric therapies as the US public health pamphlet on CFS recommends.³ ■

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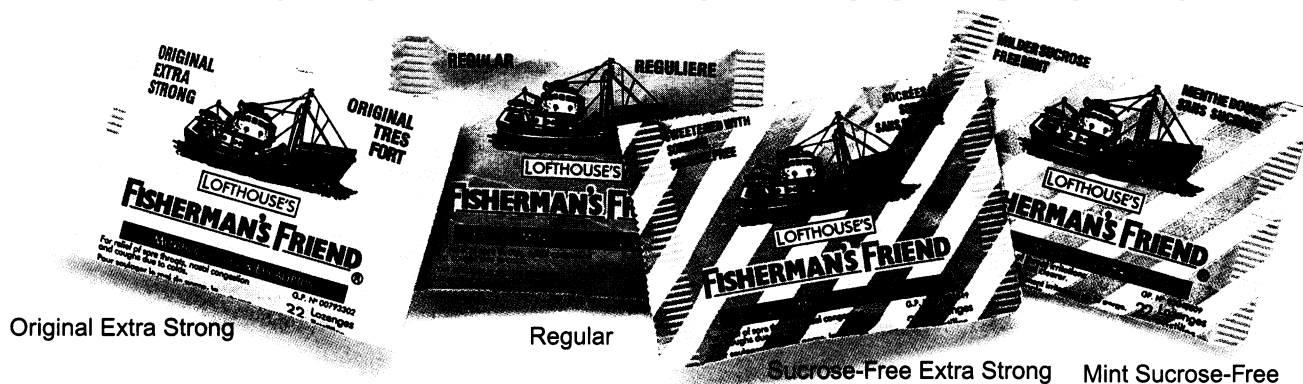
References

1. Holmes GP, Kaplan JE, Gantz NM, Komaroff AL, Schonberger LB, Straus SE, et al. Chronic fatigue syndrome: a working case definition. *Ann Intern Med* 1988;108:387-9.
2. Bates DW, Schmitt W, Buchwald D, Ware NC, Lee J, Thoyer E, et al. Prevalence of fatigue and chronic fatigue syndrome in a primary care practice. *Arch Intern Med* 1993;153:2759-65.
3. US Department of Health and Human Services. *Chronic fatigue syndrome: a pamphlet for physicians*. Washington, DC: National

Institutes of Health; 1992 publication No. 92-484.

4. Scott S, Deary I, Pelosi AJ. General practitioners' attitudes to patients with a self diagnosis of myalgic encephalomyelitis. *BMJ* 1995;310:508.
5. Kaslow JE, Rucker L, Onishi R. Liver extract-folic acid-cyanocobalamin vs placebo in chronic fatigue syndrome. *Arch Intern Med* 1989;149:2501-3.
6. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-98.
7. Parnetti L, Senin U, Carosi M, Baasch H. Mental deterioration in old age: results of two multicentre clinical trials with nimodipine. *Clin Ther* 1993;15(2):394-406.
8. March L, Irwig L, Schwarz J, Simpson J, Chock C, Brooks P. N of 1 trials comparing a non-steroidal anti-inflammatory drug with paracetamol in osteoarthritis. *BMJ* 1994;309(6961):1041-5.

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